REMARKS

1. Status of the Claims

Claims 27-30 and 32-36 are pending and have been rejected.

No new matter has been added.

2. Rejections under 35 U.S.C. § 103, obviousness

The Examiner rejects claims 27-30, 32, and 34-36 as unpatentable over Robinson, the Merck Manual, and Hattori. The Examiner also rejects claims 27-30 and 32-36 as unpatentable over Robinson, the Merck Manual, and Hattori, and further in view of Anderlini and Carmeliet. Applicants respectfully traverse.

1. There is no *prima facie* showing of obviousness.

a. Robinson and Hattori teach away from administering the recombinant protein.

The Examiner states at page 11, beginning at line 11:

> Robinson teach that G-CSF is widely used to mobilize stem cells, for example (abstract). Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells, that the mobilization of hematopietic cells followed the kinetics of placental growth factor plasma elevation (page 844 last paragraph to page 845 first paragraph and figure 4) and that PlGF provides a novel strategy for use after chemotherapy (page 842 first column). Thus, the prior art teach positive results for each of the components.

However, Robinson actually teaches away from administering protein and bolus injections. Specifically, Robinson teaches that "the direct administration of recombinant GCSF protein results in significant fluctuation in serum concentrations, as release from the injection site and clearance from the circulation occurs rapidly" (Robinson page 537, column 2, lines 22-27). Thus, one of skill in the art would expect that the direct administration of GCSF would not be useful.

Robinson also teaches that the goal is to achieve clinical efficacy with fewer injections while a bolus injection of recombinant protein is not effective. *Id.* However, Hattori teaches that in order to increase blood cell mobilization to a very high degree, a single intravenous administration (i.e., a bolus injection) of AdPlGF is necessary. Thus, one of skill in the art would not expect that 1) administration of a recombinant protein would be effective, and 2) that a bolus injection, like that of Hattori, would be effective. Thus, because Robinson suggests that applying GCSF and PlGF as in the disclosed invention would not work, Robinson teaches away from the present invention.

b. Based on Hattori, one of skill in the art would be led to an inoperative composition, and would have no expectation that combining the inoperative PlGF with GCSF would be effective.

i. Applicants have demonstrated that the PlGF protein is ineffective when administered alone.

As shown in the Examples in the Specification, and as also outlined in the enclosed Declaration, the Applicants have found that both rmPlGF and rhPlGF when administered as the sole active ingredient, are **completely inactive**.

In fact:

- in Example 2 of the present application, it is reported that mice treated intraperitoneally with 5 μg /day for 5 days with recombinant mouse PlGF (rmPlGF) show almost the same mean frequency (8±1 CFC/10^5MNCs) of circulating CFCs as the control mice (8±3 CFC/10^5MNCs) treated with PBS/MSA (See table 2).

- Example 3 of the present application reports that mice treated intraperitoneally with 5 μg /day for 5 days with recombinant mouse PlGF (rmPlGF) exhibit almost the same absolute number (96 ± 13) of circulating CFCs of control mice (81 ± 75). (See table 3).

- Example 6 of the present application reports that mice treated intraperitoneally with 10 μg/day recombinant human PlGF (rhPlGF) for 5 days exhibit almost the same mean frequency (10 ± 4) CFCs of control mice (8 ± 3). (See table 6).

- Example 7 of the present application reports that mice treated intraperitoneally with 10 μg/day recombinant human PlGF (rhPlGF) for 5 days exhibit almost the same mean absolute number (82 ± 64) of circulating CFCs of control mice(81 ± 75). (See table 7).

In Hattori a single intravenous administration of the adenoviral vector expressing the recombinant human PlGF is able:

- to induce a 20 fold increase of CFU-S/10^5PBMCs (see page 845 lines 4-6 left column) as compared with control mice three days after adenoviral infection (figure 4c),

- to induce a 14 fold increase in the total number of circulating progenitor cells in AD-PlGF treated mice if compared with Ad-Null (progenitors cells capable of forming CFU colonies) (CF-GEMM, CFU-M, BFU-E) in BALB/c mice three days after a single intravenous administration (see figure 4b and comments thereof in the legend of the figure).

As well outlined in the enclosed Declaration, one of skill in the art knows very well that the adenoviral system is a "facilitated" system of administration of a growth factor compared to administration of the same factor as such. In fact, in AdPlGF the adenovirus acts as a selective delivery system for PlGF, that is able to transport PlGF cDNA into specific target cells and to induce the expression of the growth factor. This facilitating effect exerted by the adenovirus is, on the contrary, not present in a clinical setting, where PlGF is administered as a protein.

b. **The Examiner's reliance on the administration route of Robinson disregards that the embodiment the Examiner would combine with Robinson is ineffective.**

It follows from the above that, when the Examiner argues that the instant invention is obvious by the combination of Robinson with Hattori, he impermissibly disregards evidence that overcomes Hattori: i.e., that **PlGF when used alone is completely ineffective in mobilizing blood cells.**

Consequently one of skill in the art would **not** have had any reasonable expectation from the combination of Robinson and Hattori that the claimed invention would be effective. Rather from the Hattori teaching that AdPlGF is very active in increasing blood cells mobilization, (s)he would have been motivated to think that that administration of PlGF protein alone, would also increase blood cell mobilization. **However this is not the case as pointed out above.**

c. One of skill in the art would not equate administration of AdPlGF to administration of PlGF protein.

The Examiner combines Robinson and Hattori by stating on page 5, last paragraph:

> Since Robinson teaches that GCSF can be administered by infusion or injection(abstract, page 535 2nd column) one would be motivated to formulate G-CSF and PlGF combination in such forms . . ..

In order to strengthen his arguments the Examiner relies on the 2141 Section of MPEP and the KSR decision (*KSR Int'l Co. v. Teleflex, Inc.,* 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385, 1397 (2007))[1] stating at page 9, beginning at line 21:

> [A]lthough Hattori teach the use of an adenovirus one of skill in the art would not be limited to use of an adenovirus as a method of delivering a protein. Since Robinson teach that G-CSF can be administered by infusion or injection(abstract, page 535 2nd paragraph) one would be motivated to formulate G-CSF and PlGF in such forms, for ease of administration for example. In other words, one would be motivated to standardize the mode of administration so that GCSF and PlGF could be co-administered. One of skill in the art would recognize that the active protein ingredient, that is expressed via the adenovirus (i.e. PlGF), is an active protein ingredient like that which is delivered directly via injection of a protein for example (i.e., PlGF).

Applicants respectfully traverse the Examiner's rejection since, as pointed out above, one of skill in the art knows very well that the adenoviral system is not a conventional type of administration of a protein but rather a "facilitated" system of administration of a growth factor

[1] "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton" KSR 550 U.S. at__, 82 USPQ2D at 1397. "In many cases a person of ordinary skill will be able to fit the teachings of multiple patents together to fit the teachings of multiple patents together like pieces of a puzzle" Id. Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ" Id at ___,82 U.S.P.Q.2d at1396. (Office Action, page 9).

compared to administration of the same factor as such. Therefore, one of skill in the art would not consider it equivalent to the claimed administration which applies recombinant PlGF.

In fact, as discussed above and in the enclosed Declaration, Applicants have demonstrated that PlGF administered intraperitoneally as such and as the sole active ingredient daily for 5 days **is inactive in mobilizing stem cells**.

In view of the foregoing Applicants submit that although the skilled person "is not automaton but a person of ordinary skill in the art," (*KSR*, 82 U.S.P.Q.2d at 1397) and presumably "able to fit the teachings of multiple patents together like pieces of a puzzle," (*Id.*) the Examiner **must also consider the technical knowledge** of one of skill in the art in the relevant technical field. As clearly expressed in the enclosed Declaration, this technical knowledge would not lead one to the expectation that the claimed invention would be effective, and would lead one to recognize that the results obtained by the claimed invention are unexpected. Accordingly, Applicants request that the rejection be withdrawn.

As discussed above, one of skill recognizes that administration as an adenovirus vector is different from administration as a protein. In other words the skilled person knows that an adenoviral system is a facilitated system of administration of a growth factor.

It follows from the above that the Examiner's is incorrect in stating that "although Hattori teaches the use of an adenovirus, one of skill in the art would not be limited to use an adenovirus as a method of delivering a protein."

In fact, while one of skill in the art would recognize that the active protein ingredient that is expressed via the adenovirus is the same protein ingredient like that which is delivered by injection, when PlGF is injected intraperitoneally as the sole active ingredient, is **inactive** in mobilizing blood cells.

In view of the foregoing Applicants conclude that the teachings of Robinson (that GCSF can be administered by infusion or injection), cannot be combined with the teachings of Hattori (that AdPlGF is effective in mobilizing blood) and would not have led the skilled person to formulate the claimed combination of GCSF and PlGF by injection or infusion.

d. "Consisting Essentially Of" excludes the administration of AdPlGF.

With regard to claim 35, the Examiner states that the "consisting essentially of" is construed to be equivalent to "comprising" because "there is no clear indication in the specification or claims as to what the basic and novel characteristics are." (Office Action page 6). Applicants respectfully disagree. The Specification points out that "substitutes or adjuncts to rhG-CSF either failed to substantially improve the mobilization of blood progenitors achieved with rhG-CSF alone, or resulted in a limited improvement outweighed by substantially increased toxicity" (Specification, page 3, lines 14-16) and "the administration of growth factors following injection of recombinant adenoviral vectors present several major differences from the direct injection of the purified factor." (Specification, page 6, lines 23-25). Thus, the Specification provides ample evidence that the recombinant growth factors are intended to be administered without adjuncts or adenovirus. Therefore, Applicants request that the rejection of claim 35 be withdrawn.

e. Based on the combination of Robinson and Hattori, one of skill in the art would have no reasonable expectation of success that rm or rh PlGF would be effective in combination with GCSF.

In conclusion, one of skill in the art would have no reasonable expectation that the presently claimed invention would work because:

- Robinson teaches away from using recombinant protein alone and from using bolus injection, and

- Because Hattori would lead one of skill in the art to test an inoperative composition, and one of skill in the art would have no reason to combine an inoperative composition with GCSF.

Therefore, the Examiner has failed to establish a *prima facie* case of obviousness. Applicants request that the rejection be withdrawn.

2. The present invention demonstrates unexpected results.

a. The Examiner is improperly comparing the present invention to the AdPlGF of Hattori.

Applicants submit that the Examiner's dismissal of the evidence of unexpected results is inappropriate because it applies an invalid comparison between the PlGF of Hattori to the claimed invention, and because the Examiner has inconsistently applied the data from Hattori.

i. The proper comparison is between rmPlGF alone and rmPlGF in combination with GCSF.

The Examiner uses the data from Hattori regarding AdPlGF to discredit the unexpected nature of the results achieved with PlGF protein in combination with GCSF. However, as discussed above, one of skill in the art would not make this comparison.

Instead the proper comparison is between PlGF protein alone and PlGF protein in combination with GCSF. As discussed above, the administration of PlGF protein alone does not work. Therefore, at best, one of skill in the art might expect that the combination has only the effect of GCSF alone. At worst, one of skill in the art would expect that the combination does not work at all.

As mentioned in the Specification, the effect of the combination is greater than the effect achieved with GCSF alone. Therefore, one of skill in the art would find the synergistic effect of the combination of GCSF and PlGF to be unexpected.

ii. The Examiner's reliance on the data from Hattori to deny unexpected results is inconsistent with denying Applicants' reference to the same data to show that one of skill in the art would have no reasonable expectation of success in obtaining the invention based on the combination of Robinson and Hattori.

The Examiner States on page 10, 1st full paragraph:

> Although the Applicants try to make comparisons between the instant specification and the prior art, it is noted that numerous variables are different in the experiments which could account for any differences. Further although Applicants argue the specification warns that an adenovirus might not be predictive of direct injection it is noted that section 2145 of the MPEP states: "An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."

As clearly indicated in the experimental part of the instant Specification, in the enclosed Declaration and as discussed above, the advantages obtained with the invention are demonstrated by conducting a **correct comparison** between the results obtained following administration of the sole rm or rh PlGF with PlGF in combination with G-CSF.

The Examiner concludes that the Applicants make an incorrect comparison between AdPlGF administered intravenously and PlGF administered intraperitoneally. Applicants respectfully disagree

Applicants submit that the only statistically valid comparison which can be made is between the results obtained with PlGF protein administered intraperitoneally as the sole active substance, and the same active ingredient administered in the same manner, but with the sole difference that GCSF is also associated.

The comparison made between:

a) the results obtained with Hattori reporting that a **single** administration of the adenoviral vector expressing the recombinant human PlGF is able to induce: a 20 fold increase of

CFU-S/10^5PBMCs, and a 14 fold increase in the total number of circulating progenitor cells,

b) and those obtained by administering the growth factor as such as the sole active ingredient daily for 5 days and highlighting that this active ingredient is inactive,

demonstrate only that AdPlGF and recombinant PlGF are different and **in no way comparable.** Moreover, the results demonstrate that the striking differences between ADPlGF and PlGF cannot be ascribed solely to the different type of administration. Even further, the comparison between intraperitoneal administration of PlGF protein alone vs. intravenous administration of AdPlGF is valid because both are parenteral injections.

Also, it is inconsistent to use the results of Hattori to show that PlGF would be effective in the presently claimed method while denying Applicants the opportunity to point out that the methods of Hattori are not predictive of the effectiveness of the claimed method. The Examiner states that the Applicants are not permitted to make a comparison between AdPlGF of Hattori and the administration of recombinant PlGF because they are administered by different administration routes, yet on the other hand asserts on page 11, beginning at line 2 that:

> Regardless of the experimental differences, since Hattori teach that placental growth (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed kinetics of placental growth factor plasma elevation. . . one would have a reasonable expectation of success.

Applicants emphasize that the correct comparison cannot be made between the present invention and Hattori. Instead the only valid comparison is between the present invention and the administration of the PlGF protein alone.

These assertions are not "mere attorney argument" as suggested by the Examiner. Instead the statements are based in the experimental results shown in the Specification, and supported by the Declaration.

Therefore starting from the fact that PlGF protein, when administered as the sole active ingredient, is ineffective in increasing blood cell mobilization, Applicants maintain that there was **no** reasonable expectation of success that the same factor, when administered in association with GCSF, would have been able to increase to a high degree the blood cells mobilization obtained with the latter.

b. Applicants have demonstrated the differences between mouse and human PlGF, and there is no reason to expect that Applicants' conclusions are invalid based on data variability.

The Examiner states on page 10 beginning at line 19:

> In the instant case, applicants refer to differences in which a mouse PlGF is used (example 2 of specification) and then go on to say (page 9 of reply 2/17/09) that the mouse and human PlGF behave somewhat differently. . . . As such there are numerous possible reasons for experimental variability.

The Examiner has provided no evidence that the experimental examples are not valid. Based on the discussion above, the experimental examples of the Specification **show no experimental variability which might jeopardize the validity of these experiments.** While the Examiner suggests that there are "numerous possible reasons" for experimental variability, there is no reason to suggest that recombinant PlGF in the hands of another artisan would be expected to be effective. Therefore, there is no reason to suggest that one of skill in the art would expect the presently claimed invention to be effective.

Furthermore, the Examiner is not permitted to substitute his judgment for that of one of skill in the art. "Office personnel should not . . . summarily dismiss [evidence of secondary considerations] as not compelling or insufficient. If the evidence is deemed insufficient to rebut the *prima face* case of obviousness, Office personnel should specifically set forth the facts and reasoning that justify" a conclusion that evidence of secondary considerations is insufficient to overcome a *prima face* case of obviousness. MPEP § 2145. In this instance, the Examiner has

simply assumed that an intravenous administration of a different composition would be equivalent to administration of one portion of the present invention. Moreover, the Examiner has simply discounted the evidence in the Specification which shows that the Examiner's assumption of equivalency is incorrect.

Accordingly, Applicants submit that the evidence in the Specification and in the Declaration are valid and overcome any *prima facie* case of obviousness that may have been established.

3. The Specification and the Declaration show unexpected results which overcome any *prima facie* showing of obviousness.

a. The route of administration does not obviate the showing of unexpected results.

The Declaration also highlights the striking difference of behavior on blood cell mobilization, following AdPlGF and rmPlGF administration.

The difference between the 20 fold increase in circulating progenitor cells after administration of AdPlGF compared to the intraperitoneal administration of PlGF protein alone cannot be ascribed solely to the different administration route. Rather, the difference should be attributed to the intrinsic nature of the two substances.

In fact both administration routes are indeed *parenteral injections* and IP injection is predominantly used in animal testing for the administration of systemic drugs and fluids due to the ease of administration as compared with other parenteral methods.

b. The degree of the showing of unexpectedness is sufficient to overcome any showing of *prima facie* obviousness.

The Examiner states on page 11, beginning at line 9 that:

> Although Applicants argue that one would have not been able to predict the synergistic activity and the unexpected result is evidence of unobviousness, section 716.02(a) of the MPEP states: "However a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent and that the results are of a significant, practical advantage."
>
> In the instant case Robinson teach G-CSF is widely used to mobilize stem cells, for example (abstract). Hattori teach that placental growth factor (PlGF) augments the number of circulating hematopoietic cells and that the mobilization of hematopoietic cells followed the kinetics of placental growth factor plasma elevation . . . and that PlGF provided a novel strategy for use after chemotherapy. Thus the prior art teach positive results for each of the components. Further Hattori teach that PlGF augmented the number of pluripotent hematopietic cells by 20 fold. . . . As such one would expect an increase when using PlGF. Since Hattori teach 20 fold increases, the 1.5 fold increases are not deemed unexpected, even if one accepted that increases might vary based on the mode of administration. In the instant case, the teachings of the prior art lead to a general expectation of increases when PlGF is used.

Once again, the correct comparison between the instant invention cannot rely on the quantitative results of Hattori which demonstrates stimulation of blood cell mobilization with AdPlGF. Instead the correct comparison is against PlGF protein when administered alone.

The Declaration clearly explains the surprising effects obtained with the combined administration of GCSF and PlGF, clearly evidencing that, although PlGF as such, when administered intraperitoneally alone, **is completely inactive**, PlGF when associated with GCSF is able to increase to a high degree the mobilization of blood cells and more. In particular the Declaration shows that:

- as reported in Example 2, while PlGF administered alone is inactive, the same, when administered intraperitoneally at the same dosage (5μg/day) and with the same modalities (for 5 days) in association with G-CSF, is able to increase the frequency of CFCs of about 1.4 folds that obtained after administration of the sole G-CSF.

- as reported in Example 3, while rm PlGF administered alone is inactive, the same, when administered intraperitoneally at the same dosage (5μg/day) and with the same modalities (for 5 days) in association with G-CSF, is able to increase a number of circulating CFCs in mice of 2 folds that obtained with the sole G-CSF.

- As reported in Example 6, while recombinant human PlGF administered alone is inactive, the same, when administered intraperitoneally at the same dosage (10μg/day) and with the same modalities (for 5 days) in association with G-CSF, is able to increase the mean frequency of CFCs of more than three folds (3.12) that obtained after administration of the sole G-CSF (see example 6). Moreover as demonstrated in the same example rhPlGF, also when administered at a dosage of only 5 μg/day in association with G-CSF is able to increase the mean frequency of CFCs to a mean frequency of almost three folds (2.73) that obtained with rhGCSF alone.

- as reported in example 7, while rhPlGF administered alone is inactive, the same, when administered intraperitoneally at the same dosage (10μg/day) and with the same modalities (for 5 days) in association with G-CSF, is able to increase the absolute number of circulating CFCs in mice to a mean absolute number of circulating blood cells 4 folds that obtained with the sole G-CSF. Moreover as demonstrated in the same example rhPlGF, also when administered at a dosage of only 5 μg/day in association with G-CSF is able to increase the absolute number of circulating of about two folds (2.17) if compared to those obtained with the sole G-CSF.

The results discussed above strongly support a finding of unexpectedness and demonstrate a high degree of blood mobilization considering that PlGF protein and administered alone **by the same route and with the same modalities is inactive**.

Applicants, finally conclude that the Examiner's assertion that since Hattori teaches that PlGF augmented the number of pluripotent hematopoietic cells by 20 fold increases, the 1.5 increases are not deemed unexpected, is not scientifically correct.

In fact the closest type of administration to the invention is not the administration of AdPlGF, but rather the administration of the PlGF as such, which **as above stated is inactive.**

Applicants submit that because the association of PlGF with GCSF is able to increase cell mobilization by 1.4 fold, or in some cases 4 fold as compared with that obtained with GCSF alone, **this finding completely satisfies the requirements of MPEP 716.02.**

Accordingly, Applicants submit that the invention is not obvious in view of the combination of Robinson and Hattori. Applicants respectfully request that the rejection be withdrawn.

With regard to references Anderlini and Carmeliet, the Examiner concedes that neither reference teaches the claimed composition or even purified PlGF and GCSF separately as it is used in the composition and method of the present invention. Accordingly, based on the arguments discussed above and the Examiner's own understanding of the additional references, one of skill in the art would not have found the present invention obvious. Thus, Applicants request that the Examiner withdraw the rejection.

Conclusion

In view of the above remarks, it is believed that claims are allowable.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee of $1,100.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell Reg. No. 36,623 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

#47,604

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